AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning on page 4, line 6 as follows:

Recently, a humanized murine anti HER-2/neu monoclonal antibody (MAb) 4D5 ~~to HER-2/neu~~, ~~Herceptin~~ (HERCEPTIN®), has been reported to have significant therapeutic effects in patients with strongly (i.e., score 2+ and 3+) HER-2/neu-positive breast carcinomas, particularly when combined with chemotherapeutic drugs (17,18). In ovarian, lung cancer and prostate cancers, clinical studies are currently investigating the efficacy of HERCEPTIN® ~~Herceptin~~ in patients whose tumors exhibit strong plasmalemmal immunoreactivity for this protein (19). In contrast to ovarian cancer, however, very little is known about HER-2/neu expression by the histologically similar but biologically more aggressive uterine serous papillary carcinoma.

Please amend the paragraph beginning on page 5, line 4 as follows:

The present invention reports that a variant of uterine cancer commonly overexpresses HER-2/neu (i.e., score 2+ or more in 80% of samples tested), and that the levels of protein expression on primary uterine serous papillary carcinoma cell lines recorded by flow cytometry are on average 10-fold higher when compared to fresh or established breast and ovarian HER-2/neu positive cancer cell lines. Importantly, although uterine serous papillary carcinoma

cell lines are resistant to natural killer dependent cytotoxicity *in vitro*, they retain high sensitivity to anti-HER-2/neu antibody dependent cellular cytotoxicity (ADCC), and that their *in vitro* proliferation is significantly inhibited by a humanized murine anti-HER2/neu monoclonal antibody (~~Herceptin~~HERCEPTIN®). Furthermore, a significant enhancement of antibody dependent cellular cytotoxicity was demonstrated when peripheral blood effector cells were incubated with uterine serous papillary carcinoma cells in the presence of low doses of IL-2. Thus, ~~Herceptin~~HERCEPTIN® therapy is a therapeutic strategy in patients harboring this biologically aggressive and chemotherapy and radiotherapy-resistant variant of endometrial cancer.

Please amend the paragraph beginning on page 8, line 10 as follows:

Figure 2 shows a representative FACS analysis of ~~Herceptin~~HERCEPTIN® (humanized murine anti-HER-2/neu monoclonal 4D5) staining of primary uterine serous papillary carcinoma cells, primary and established ovarian and breast cancer cell lines. Data with ~~Herceptin~~HERCEPTIN® are shown in solid black while isotype control monoclonal antibody profile are shown in white. Similar results were obtained with FITC-labeled antiHER-2/neu monoclonal antibody (Oncogene Science) stained tumor cell lines (data not shown). HER-2/neu expression was significantly higher on uterine serous papillary carcinoma cell lines compared to fresh and established ovarian cancer cell lines and established breast cancer cell lines ($p < 0.001$ by student *t* test).

Please amend the paragraph beginning on page 9, line 1 as follows:

Figure 3 shows antibody dependent cellular cytotoxicity mediated by ~~Herceptin~~HERCEPTIN® (2 mg/ml) against ^{51}Cr-labeled USPC-1 (upper panel) and USPC-2 (lower panel) cells (10,000 cells/sample), as measured in combination with effector peripheral blood lymphocytes from a representative healthy, heterologous donor in a 5 hrs assay. The figure shows the percentage of target cell lysis (± SD). Effector cells plus ~~Rituxan~~RITUXAN® (2 mg/ml) were used as controls. Similar antibody dependent cellular cytotoxicity results were obtained with the use of ~~Herceptin~~HERCEPTIN® at 1 or 5 mg/ml (data not shown).

Please amend the paragraph beginning on page 9, line 12 as follows:

Figure 4 shows antibody dependent cellular cytotoxicity mediated by ~~Herceptin~~HERCEPTIN® (2 mg/ml) against ^{51}Cr-labeled USPC-3 cells (10,000 cells/sample), as measured in combination with autologous effector peripheral blood lymphocytes in a 5 hr assay. The figure shows the percentage of target cell lysis (± SD). Peripheral blood lymphocytes plus medium only, or ~~Rituxan~~RITUXAN® (2 mg/ml), were used as controls. Similar antibody dependent cellular cytotoxicity results were obtained with the use of ~~Herceptin~~HERCEPTIN® at 5 mg/ml (data not shown).

Please amend the paragraph that begins on page 10, line 2 as follows:

Figure 5 shows the effect of complement and serum immunoglobulin (dilution 1: 2) on cytotoxicity mediated by ~~Herceptin~~HERCEPTIN® (2 mg/ml) against ^{51}Cr-labeled USPC-1 (**Figure 5A**, **Figure 5C**, **Figure 5E**) and USPC-2 (**Figure 5B**, **Figure 5D**, **Figure 5F**) cells (10,000 cells/sample), measured in the presence or absence of effector peripheral blood lymphocytes from a representative heterologous healthy donor in a 5 hr assay. The figure shows the percentage of target cell lysis (± SD) at E/T ratios 25 : 1. Effector peripheral blood lymphocytes with medium alone, or with ~~Rituxan~~RITUXAN® (2 mg/ml) plus or minus serum were used as controls. ~~Herceptin~~HERCEPTIN®-mediated antibody dependent cellular cytotoxicity in the presence of heat-inactivated human serum and effector peripheral blood lymphocytes was not significantly different to the results obtained in the absence of serum. ~~Herceptin~~HERCEPTIN®-mediated antibody dependent cellular cytotoxicity in the presence of untreated human serum and effector peripheral blood lymphocytes was significantly increased compared to the results obtained in the absence of serum ($p < 0.03$).

Please amend the paragraph beginning on page 11, line 1 as follows:

Figure 6 shows enhancement of antibody dependent cellular cytotoxicity mediated by ~~Herceptin~~HERCEPTIN® (2 mg/ml)

against ^{51}Cr-labeled USPC-2 cells (10,000 cells/sample) in the presence of 100 IU/ml of IL-2 for 5 hr (upper panel) or following pre-incubation of effector peripheral blood lymphocytes with 100 IU/ml of IL-2 for 72 hr (lower panel), as measured in a 5 hr assay. The figure shows the percentage of target cells lysis (± SD) at E/T ratios 50 : 1. Effector peripheral blood lymphocytes with medium only, or in the presence of ~~Rituxan~~RITUXAN® (2 mg/ml) were used as controls. ~~Herceptin~~HERCEPTIN®-mediated antibody dependent cellular cytotoxicity was significantly enhanced ($p < 0.01$ by student t test). A small but significant increase in cytotoxic activity was seen at 72 hr of IL-2 exposure in the absence of ~~Herceptin~~HERCEPTIN® and in the presence of ~~Rituxan~~RITUXAN® ($p < 0.05$). Similar results were obtained after incubation of effector peripheral blood lymphocytes with 50 IU/ml of IL-2.

Please amend the paragraph beginning on page 12, line 3 as follows:

The instant invention is directed to a method of treating uterine serous papillary carcinoma in an individual in need of such treatment, comprising the step of administering to said individual a therapeutically effective dose of a HER-2/neu antibody. Preferably, the antibody is a monoclonal antibody and even more preferably the antibody is a humanized monoclonal antibody. A representative example of an antibody useful in the methods of the present invention is the humanized murine anti-HER-2/neu monoclonal antibody 4D5 (HERCEPTIN®) ~~Herceptin®~~. A person having ordinary

skill in this art would readily recognize suitable dosages of an antibody useful in these methods. For example, the ~~Herceptin~~HERCEPTIN® antibody is administered in a dose of from about 4 mg/kg to about 8 mg/kg. This method further comprises the step of administering a therapeutically effective dose of interleukin-2 to said individual. Generally, the interleukin-2 is recombinant interleukin-2. Preferably, the dose of interleukin-2 is very low and non-toxic. For example, interleukin-2 may be administered to an individual in a dose of from about 1 x 10^6 IU/M^2 to about 10 x 10^6 IU/M^2.

Please amend the paragraph beginning on page 13, line 8 as follows:

The instant invention is also directed to a method of treating uterine serous papillary carcinoma in an individual in need of such treatment, comprising the step of administering to said individual a therapeutically effective dose of a HER-2/neu antibody and a therapeutically effective dose of interleukin-2. Preferably, the HER-2/neu antibody is a monoclonal antibody and even more preferably is a humanized monoclonal antibody. Most preferably, the HER-2/neu antibody is ~~Herceptin~~HERCEPTIN®. Generally, the HER-2/neu antibody may be given in any therapeutically effective dose but preferably the antibody is administered to the individual in a dose of from about from about 4 mg/kg to about 8 mg/kg. Preferably, the interleukin-2 is recombinant interleukin-2 and is administered to the individual in a dose that is non-toxic, for

example ~~exampl~~, a dose of from 1 x 10^6 IU/M^2 to about 10 x 10^6 IU/M^2.

Please amend the paragraph beginning on page 18, line 5 as follows:

The clinically marketed anti-HER-2/neu monoclonal antibody ~~Herceptin~~HERCEPTIN® (Genentech, San Francisco, CA) was used for most of the study. For comparison, an unconjugated anti-HER2/neu (mouse IgG1) monoclonal antibody obtained from Oncogene Science (Uniondale, NY) was used. ~~Herceptin~~HERCEPTIN® is an IgG1k that contains human framework regions with the complementary-determining regions of a murine monoclonal antibody that binds to the Mr 185,000 extracellular determinant of HER-2/neu. For staining by ~~Herceptin~~HERCEPTIN®, a FITC-conjugated goat anti-human F(ab^1)2 immunoglobulin was used as a secondary reagent (BioSource International, Camarillo, CA). For staining by unconjugated anti-HER-2/neu (mouse IgG1) a goat anti-murine FITC labeled mouse IgG1 (Beckman-Coulter Miami, FL) was used. Analysis was conducted with a FACScan, utilizing cell Quest software (Beckton Dickinson).

Please amend the paragraph beginning on page 19, line 4 as follows:

A standard 5-hour chromium (^{51}Cr) release assay was performed to measure the cytotoxic reactivity of Ficoll-Hypaque separated peripheral blood lymphocytes (PBL) from several healthy

donors and one uterine serous papillary carcinoma patient in combination with anti-HER-2/neu antibody ~~Herceptin~~ against tumor target cell lines. The release of ^{51}Cr from the target cells was measured as described (22) as evidence of tumor cell lysis, after exposure of tumor cells to varying concentrations of anti-HER-2/neu ~~Herceptin~~HERCEPTIN® (ranging from 1 mg/ml to 5 mg/ml). Controls included the incubation of target cells alone or with peripheral blood lymphocytes or monoclonal antibody separately. The chimeric anti-CD20 monoclonal antibody Rituximab (~~Rituxan~~RITUXAN®, Genentech, CA) was used as control for ~~Herceptin~~HERCEPTIN® in all bioassays. ~~antibody~~ Antibody dependent cellular cytotoxicity was calculated as the percentage of killing of target cells observed with monoclonal antibody plus effector cells, as compared with ^{51}Cr release from target cells incubated alone.

Please amend the paragraph beginning on page 21, line 4 as follows:

To investigate the effect of IL-2 on anti-HER-2/neu~~Herceptin~~-mediated antibody dependent cellular cytotoxicity, effector peripheral blood lymphocytes were incubated at 37°C at a final concentration of IL-2 (Aldesleukin, Chiron Therapeutics, Emeryville, CA) ranging from 50 to 100 IU/ml in 96-well microtiter plates. In some experiments, effector peripheral blood lymphocytes were incubated with IL-2 only during the standard 5-hour chromium (^{51}Cr) release assay, while in other experiments effector peripheral blood lymphocytes were preincubated for up to 72 hrs with IL-2 prior to antibody dependent cellular cytotoxicity assay. Target cells

were primary uterine serous papillary carcinoma cell lines exposed to anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~ (concentrations ranging from 1 mg/ml to 5 mg/ml), while controls included the incubation of target cells alone, or with peripheral blood lymphocytes in the presence or absence of IL-2 or MAb, respectively. ~~Rituxan~~RITUXAN® was used as a control monoclonal antibody. Antibody dependent cellular cytotoxicity was calculated as the percentage of killing of target cells observed with monoclonal antibody plus effector peripheral blood lymphocytes, as compared with target cells incubated alone. Each experiment was performed with at least two normal donors, with results from a representative donor presented.

Please amend the paragraph beginning on page 22, line 9 as follows:

Primary uterine serous papillary carcinoma cell lines from patients USPC-1 and USPC-2 were plated at 2,500 cells/well in V-bottomed 96-well plates in the presence or absence of varying concentrations of anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~ on day 0, using ~~Rituxan~~RITUXAN® as a control. On day 4, cells were pulsed with [H^3] thymidine (1 mCi/well) for 6 hrs and then placed in a -20°C freezer for 1 hr. After thawing at room temperature, cells were harvested using a ~~packard~~ PACKARD® Filtermate Harvester Unifilter-96 and incorporated radioactivity was measured as described (23).

Please amend the paragraph beginning on page 26, line 3 as follows:

Uterine serous papillary carcinoma were Resistant to NK Activity but Sensitive to [[Herceptin]]HERCEPTIN®-mediated antibody dependent cellular cytotoxicity

Primary uterine serous papillary carcinoma cell lines were tested for their sensitivity to natural killer cytotoxicity when challenged with peripheral blood lymphocytes collected from several healthy donors in a standard 5 hr ^{51}Cr release assay. As shown in Figure 3, uterine serous papillary carcinoma cell lines were consistently found to be resistant to NK-mediated killing when combined with peripheral blood lymphocytes at effector: target (E/T) cell ratios varying from 12.5 : 1 to 50 : 1 (range of killing from 0 to 3% with all E/T ratios). Similarly, uterine serous papillary carcinoma cell lines incubated with ~~Rituxan~~RITUXAN® control antibody were not significantly killed (range of killing from 0 to 3% with all E/T ratios)(Figure 3). In strong contrast, uterine serous papillary carcinoma cell lines were found to be highly sensitive to peripheral blood lymphocytes from heterologous donors combined with anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~ to mediate antibody dependent cellular cytotoxicity (range of killing from 25% to 60% from 12.5:1 to 50:1 E/T ratio) (Figure 3). This experiment was repeated five times with similar results.

Please amend the paragraph beginning on page 27, line 7 as follows:

[[Herceptin]]HERCEPTIN®-Mediated antibody dependent cellular cytotoxicity By Autologous peripheral blood lymphocytes

Because in experimental models and human beings (25,26), alteration in number and function of NK cells has been associated with tumor progression, the ability of autologous peripheral blood lymphocytes from patients harboring uterine serous papillary carcinoma to kill tumor cells in the presence or absence of anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~ was investigated. The USPC-3 cell line was challenged with peripheral blood lymphocytes collected from the patient in a standard 5 hr ^{51}Cr release assay. Similarly to the results obtained using healthy donor peripheral blood lymphocytes against USPC-1 and USPC-2 cell lines (Figure 3), USPC-3 was found to be highly resistant to autologous NK-mediated killing at all the effector : target cell ratio tested (i.e., from 25 : 1 to 50 : 1, range of killing from 0 to 1% with all E/T ratios), (Figure 4). The USPC-3 cell line incubated with ~~Rituxan~~RITUXAN® (anti-CD20) control antibody was not significantly killed (range of killing from 0 to 1% with all E/T ratios) (Figure 4). In contrast, USPC-3 was found to be highly sensitive to ~~Herceptin~~HERCEPTIN® when combined with autologous peripheral blood lymphocytes to mediate antibody dependent cellular cytotoxicity (range of killing from 35 to 75% from 25 : 1 to 50 : 1 E/T ratio)(Figure 4). This experiment was repeated two times with similar results.

Please amend the paragraph beginning on page 28, line 11 as follows:

Effect of Complement and Physiological Concentrations of IgG On [[Herceptin]]HERCEPTIN®-Mediated antibody dependent cellular cytotoxicity against USPC

To evaluate primary uterine serous papillary carcinoma cell lines for their sensitivity to complement-mediated cytotoxicity, and to evaluate possible inhibition of antibody dependent cellular cytotoxicity by physiological concentrations of IgG, uterine serous papillary carcinoma cell lines were challenged by adding human serum diluted 1 : 2 to 1 : 4 (with or without heat inactivation) in the presence or absence of the effector cells and anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~ to standard 5 hr ^{51}Cr release assays.

Please amend the paragraph beginning on page 29, line 1 as follows:

As shown in Figure 5, addition of untreated serum with or without ~~Herceptin~~ HERCEPTIN® or ~~Rituxan~~RITUXAN®, was not able to induce significant cytotoxicity against USPC-1 (A,C,E) and USPC-2 (B,D,F) cell lines. These data illustrate the lack of significant cytotoxicity mediated by complement proteins in the absence of effector cells. Addition of physiological concentrations of IgG (i.e., heat-inactivated serum diluted 1 : 2 to 1 : 4) to peripheral blood lymphocytes in the presence of ~~Herceptin~~ HERCEPTIN® did not

significantly alter the degree of antibody dependent cellular cytotoxicity achieved in the presence of ~~Herceptin~~ HERCEPTIN® (Figure 5). In contrast, addition of untreated serum (diluted 1 : 2 to 1 : 4) to peripheral blood lymphocytes in the presence of ~~Herceptin~~ HERCEPTIN® consistently increased ~~Herceptin~~HERCEPTIN®-mediated cytotoxicity against uterine serous papillary carcinoma ($p < 0.03$)(Figure 5).

Please amend the paragraph beginning on page 29, line 19 as follows:

To investigate the effect of low doses of interleukin-2 (IL-2) in combination with anti-HER-2/neu antibody HERCEPTIN®-mediated ~~Herceptin~~ (2 mg/ml) ~~on~~ antibody dependent cellular cytotoxicity against uterine serous papillary carcinoma cell lines, peripheral blood lymphocytes from healthy donors were incubated for 5 hr to 72 hr in the presence of 50 to 100 IU/ml of IL-2. As representatively shown in Figure 6, ~~Herceptin~~HERCEPTIN®-mediated antibody dependent cellular cytotoxicity was significantly increased in the presence of low doses of IL-2. Administration of 100 IU/ml of IL-2 to the effector peripheral blood lymphocytes at the start of the assay increased the cytotoxic activity against uterine serous papillary carcinoma cell lines compared to the use of ~~Herceptin~~ HERCEPTIN® alone, while no significant increase in cytotoxicity was detected after 5 hrs' IL-2 treatment in the absence of ~~Herceptin~~ HERCEPTIN® or in the presence of ~~Rituxan~~RITUXAN® control monoclonal antibody (Figure 6). Longer periods of pre-incubation

(72 hr) of effector peripheral blood lymphocytes with IL-2 showed a similar increase in antibody dependent cellular cytotoxicity in the presence of ~~Herceptin~~ HERCEPTIN®. However, a small but significant increase in cytotoxicity was also detectable in the absence of ~~Herceptin~~ HERCEPTIN® and in presence of ~~Rituxan~~RITUXAN® against the uterine serous papillary carcinoma cell line tested, possibly related to lymphokine-activated killer (LAK) activity (Figure 6).

Please amend the paragraph beginning on page 31, line 3 as follows:

Growth of HER-2/neu Positive uterine serous papillary carcinoma can be Inhibited by [[Herceptin]]HERCEPTIN® in Vitro

Experiments were performed to investigate whether the proliferation of two different HER-2/neu positive uterine serous papillary carcinoma cell lines (USPC-1 and USPC-2) can be inhibited by anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~, as compared with ~~Rituxan~~RITUXAN®, which was used as a control. Data presented in Table 2 show this to be the case. The proliferation of both cell lines was significantly inhibited in the presence of HERCEPTIN® ~~Herceptin~~ with the percentage of inhibition varying from 30% to 62% for USPC-1 and from 22% to 52% % for USPC-2 ($p > 0.05$) (Table 2).

Please replace lines 4-7 on page 32 with the following lines:

Inhibition of 3Thymidine Uptake by USPC Cells Grown in the Presence of [[Herceptin]]HERCEPTIN®

Experiment No. Target Cells [[Herceptin]]HERCEPTIN® Dose % Inhibition

Please amend the paragraph beginning on page 32, line 17 as follows:

There were 6-8 replicates per group. ~~Rituxan~~RITUXAN® was used as a control monoclonal antibody and gave no inhibition when compared with culture medium alone.

Please amend the paragraph beginning on page 35, line 19 as follows:

Primary uterine serous papillary carcinoma studied were found to be highly resistant to killing by natural killer cells and partially resistant to LAK activity (i.e., peripheral blood lymphocytes cultured for up to 72 hrs in 100 IU/ml of IL-2). These data therefore demonstrated that in addition to their high resistance to chemotherapy, radiation treatment and hormonal therapy (2-7), uterine serous papillary carcinoma cells are also intrinsically highly resistant to natural killer activity. Furthermore, complement-mediated tumor cell lysis (in the absence of effector cells) was not observed, which may be due to the presence of membrane-associated complement regulatory proteins such as CD35 (complement receptor 1), CD55 (decay accelerating factor), or CD46 (membrane cofactor protein) on uterine serous papillary carcinoma, as previously reported for other human tumors resistant

to complement dependent cytotoxicity (31). In strong contrast, however, all primary uterine serous papillary carcinoma cell lines tested were found to be highly susceptible to antibody dependent cellular cytotoxicity when incubated with heterologous or autologous effector cells in the presence of anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~. These data, therefore, demonstrate that although these tumor cells are *per se* extremely resistant to any standard cytotoxic therapy in the clinic, they remain highly sensitive to the killing activity mediated by NK cells when triggered by HER-2/neu-specific antibody.

Please amend the paragraph beginning on page 37, line 1 as follows:

In vivo, antibody dependent cellular cytotoxicity applications are known to be dependent upon the availability of the effector cells to interact with the antibody at the target site in the presence of high concentrations of irrelevant human IgG. In this study, antibody dependent cellular cytotoxicity against uterine serous papillary carcinoma was not significantly inhibited by high concentrations (up to 50%) of human serum. In fact, a consistent increase in cytotoxicity was detected in the presence of effector cells and non-heat inactivated human serum. These data, therefore, suggest that in the presence of effector peripheral blood lymphocytes, human serum may augment anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~-mediated cytotoxicity against uterine serous papillary carcinoma. Moreover, these results indicate that the

binding of ~~Herceptin~~HERCEPTIN® to the Fc receptor on mononuclear effector cells is of very high affinity and is likely to occur in the *in vivo* situation.

Please amend the paragraph beginning on page 37, line 17 as follows:

Treatment of cancer patients with combinations of MAbs and cytokines does not amount to a mere addition to the benefit of each treatment modality alone, but has clearly been demonstrated to have synergistic potential (32,33). Recently, low doses of rIL-2 have been given by continuous infusion or subcutaneously, with remarkable immunologic results coupled with negligible toxicity (34,35). This point is noteworthy because, both in experimental models and in human beings, modulation of both the number and function of NK cells has been previously associated with tumor progression (25,26) and, in addition, substantially suppressed antibody dependent cellular cytotoxicity responses have been reported in several cancer patients (36). Importantly, however, cytotoxicity levels in patients who demonstrate suppressed antibody dependent cellular cytotoxicity can be increased *in vitro* to levels similar to those of normal donors by prior exposure of effector cells to IL-2 (37). Consistent with this view, a significant increase in antibody dependent cellular cytotoxicity against uterine serous papillary carcinoma was detected after exposure of effector cells from healthy donors as well as one uterine serous papillary carcinoma patient (data not shown) to low doses of IL-2 *in vitro* for

a brief time (i.e., 5 hrs). Longer time periods of incubation (up to 3 days) with IL-2 under the same conditions showed similar results. These data therefore suggest that the administration of low (i.e., non toxic) doses of IL-2 *in vivo*, giving rise to a lytic effector cell that is markedly enhanced in its function by the addition of an antibody bridge, may significantly increase the efficacy of anti-HER-2/neu antibody HERCEPTIN® ~~Herceptin~~ therapy in uterine serous papillary carcinoma patients. Furthermore, on the basis of the high resistance of uterine serous papillary carcinoma to standard cytotoxic anti-cancer therapy, these combined therapies might be particularly important in the treatment of uterine serous papillary carcinoma patients.

Please amend the paragraph beginning on page 39, line 7 as follows:

Although the majority of previous reports investigating the anti-tumor effects of monoclonal antibodies support the view that efficacy is primarily dependent on immune activation through the Fc receptor (38), others have shown that ~~Herceptin~~HERCEPTIN® retains about 40% of its anti-tumor activity in FcgRIII$^{-/-}$ mice compared to wild-type mice, indicating that some biological effects of monoclonal antibodies can be independent of Fc receptor binding (39). Consistent with these data, in this study, a significant inhibition in the proliferation of uterine serous papillary carcinoma cell lines was detected by a anti-HER-2/neu monoclonal antibody. These results demonstrated that uterine serous papillary carcinoma

behave similarly to ovarian cancer cell lines overexpressing HER-2/neu (16).

Please amend the paragraph beginning on page 39, line 20 as follows:

In conclusion, the present invention demonstrates that HER-2/neu is highly expressed by uterine serous papillary carcinoma, and that uterine serous papillary carcinoma cells are exquisitely sensitive to anti-HER-2/neu antibody HERCEPTIN®~~Herceptin~~-mediated antibody dependent cellular cytotoxicity. On the basis of these findings and previous evidence showing a correlation between efficacy of ~~Herceptin~~HERCEPTIN® therapy in direct proportion to the HER-2/neu overexpression on tumor cells one may postulate that ~~Herceptin~~HERCEPTIN® is a novel and attractive therapeutic strategy in uterine serous papillary carcinoma patients either for the prevention of recurrence after surgical treatment or for the treatment of metastatic disease. The future design and implementation of clinical trials in this regard will ultimately determine the validity of this approach.